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Organocatalytic asymmetric transformations of 3–substituted 3–hydroxyisoindolinones

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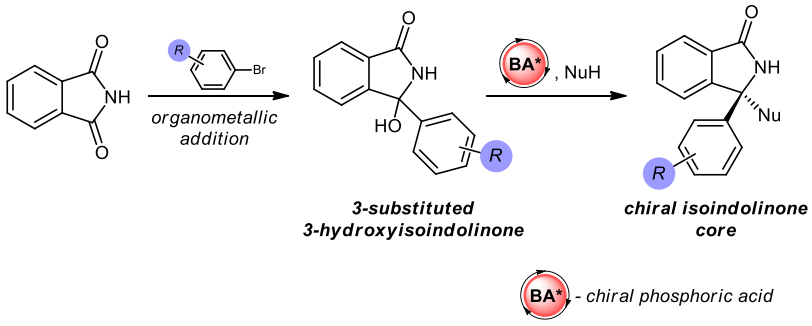


Abstract. This Account provides an overview of our group's research in the field of asymmetric organocatalytic transformations generating chiral isoindolinone cores. We describe the synthesis of 3–substituted 3–hydroxyisoindolinones, starting materials for these transformations, comprising a wide range of functional groups, as well as their utilization in asymmetric transformations. We also discuss our efforts in the application of the developed methodology in the synthesis of a known HIV–1 Inhibitor.

1 Introduction

2 Synthesis of isoindolinone alcohols comprising functional groups

3 Asymmetric organocatalytic transformations of isoindolinone alcohols

4 Conclusion

Key words. organocatalytic asymmetric transformation, 3–hydroxyisoindolinones, chiral Brønsted acid, isoindolinone core, organometallic addition, chiral N,S–acetals.

1 Introduction

3–Substituted isoindolinones and their derivatives are common structural motifs in a variety of compounds with biological activities (Figure 1). For example, they have been established as precursors to isoindolinone–derived anti–ischemic stroke agents,[1] as well as antimicrobial[2] and antitumor[3] agents. Their activity as MDM2–p53 protein–protein,[4] HIV–1 integrase,[5] and protein–tyrosine phosphatase inhibitors[6] is also well known. In addition, registered and commercially available anxiolytic,[7] anticonvulsant[8] and antihypertensive[9] drugs also contain 3–substituted isoindolinone cores. Hence, it is of great importance to develop facile and effective methods for their synthesis.

First methodologies for the synthesis of 3–substituted isoindolinones were not very effective or practical. Kundu et al. reported a multistep synthesis of isoindolinones, starting with the Sonogashira coupling between 2–iodobenzamide and trimethylsilyl acetilene, followed by Friedel–Crafts acylation, simultaneous cyclization, and finishing with catalytic hydrogenation.[10] A different approach was used by the Allin group, where 3–substituted isoindolinones were obtained by the annulation of phenylglycinol with the corresponding ketoacid, followed by Lewis acid–catalyzed ring opening.[11] On the other hand, the Enders

group generated 3–substituted isoindolinones by alkylating unsubstituted 3,3–dihydroisoindolinones, though the synthesis of the starting dihydroisoindolinone is long and low yielding.[12] Major drawbacks of these pioneer protocols are harsh reaction conditions, commercially unavailable starting materials, and multistep reactions with low overall yields.

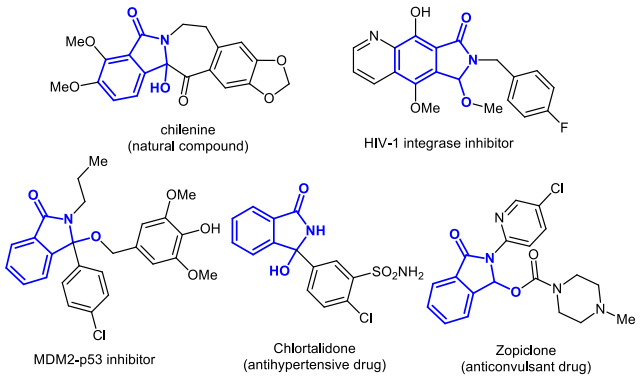
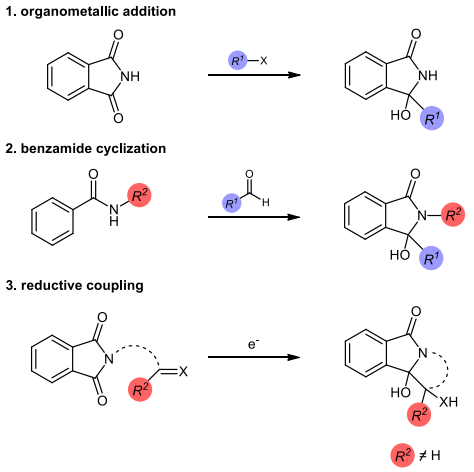


Figure 1 Examples of 3–substituted isoindolinones with biological activity.

New methodologies emerged when it was found that 3-substituted 3-hydroxyisoindolinones can easily be converted into 3-substituted isoindolinones by deoxygenation, or to 3,3-disubstituted isoindolinones by a nucleophilic attack under acidic conditions. In 2002, Wang et al. reported the first organolithium addition to phthalimides, generating 3–alkylated 3–hydroxyisoindolinones in excellent yields (Scheme 1.1).[13] Obtained alcohols were subsequently converted to corresponding 3-substituted isoindolinones by employing sodium cyanoborohydride. Huang et al. expanded this methodology by using Grignard reagents as nucleophiles.[14] Deoxygenation of isoindolinone alcohols with triethylsilane in the presence of boron trifluoride etherate afforded 3-substituted isoindolinones in excellent yields. The Johnson group reported thermal[15] and nickel-catalyzed[16] additions of diorganozinc reagents, though the protocol requires imide substitution on the starting phthalimide.

However, due to the availability of starting materials and functional group stability, these reactions mostly employ highly reactive and commercially available orgametallic reagents, such as reagents derived from alkyl halides and electron-rich phenyl rings. Hence, in order to expand the variety of functional groups that can be incorporated into the 3-substituted isoindolinone core, different protocols were required.



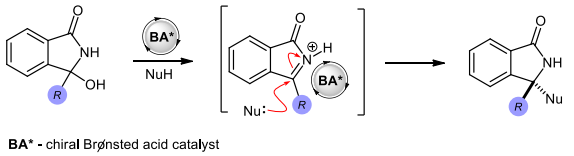
Scheme 1 Synthetic strategies for the preparation of 3-substituted 3-hydroxyisoindolinones.

One of the most used alternative strategies is the cyclization of the parent benzamide (Scheme 1.2). Kim et al. described a tandem rhodium(III)-catalyzed oxidative acylation of secondary benzamides with aryl aldehydes by sp^2 C-H bond activation, followed by an intramolecular cyclization,[17] while the Zhao group reported the same transformation by using palladium acetate as a catalyst.[18] Recently, Li et al. also employed palladium acetate for the synthesis of 3-substituted 3-hydroxyisoindolinones by annulation reactions of benzamides with phenylglyoxylic acids.[19]

Isoindolinone alcohols can also be prepared with reductive coupling reactions (Scheme 1.3). Chiara et al. showed that phthalimides are highly efficient single electron transfer acceptors, and could be used in reactions promoted by samarium diiodide.[20] Formed ketyl radical anion participates in high-yielding reductive coupling processes with different radicophiles. The Kise group built on this principle, and reported electroreductive coupling of phthalimides with aldehydes in the presence of chlorotrimethylsilane and triethylamine.[21] Authors expanded this methodology to the reductive coupling of phthalimides with aldehydes and ketones by using low-valent titanium.[22] The latter reaction furnished two- and four-electron reduced products, 3-hydroxyisoindolinones and 3-alkylideneisoindolinones, which could be obtained selectively by controlling the reaction conditions. Other methods for obtaining isoindolinone alcohols include inter-[23] and intramolecular[24] photodecarboxylative additions of carboxylates to phthalimides, and fluoride-catalyzed nucleophilic additions.[25]

Although described protocols offer elegant and functional group tolerant methods for the preparation of substituted isoindolinones, they suffer from certain drawbacks: employment of expensive catalysts, oxidants, exotic reagents, and tedious reaction conditions. However, probably the biggest limitation of these methods is that the final isoindolinone alcohols are obtained as *N*-substituted products. *N*-substitution is required in the starting materials, since it plays a significant role in the formation of products. In metal-catalyzed reactions, the substituent often serves as metal coordination site, thus limiting the reaction scope. In several examples it plays a role in the solubility of precursors, or the transformation does not tolerate nitrogen atom.

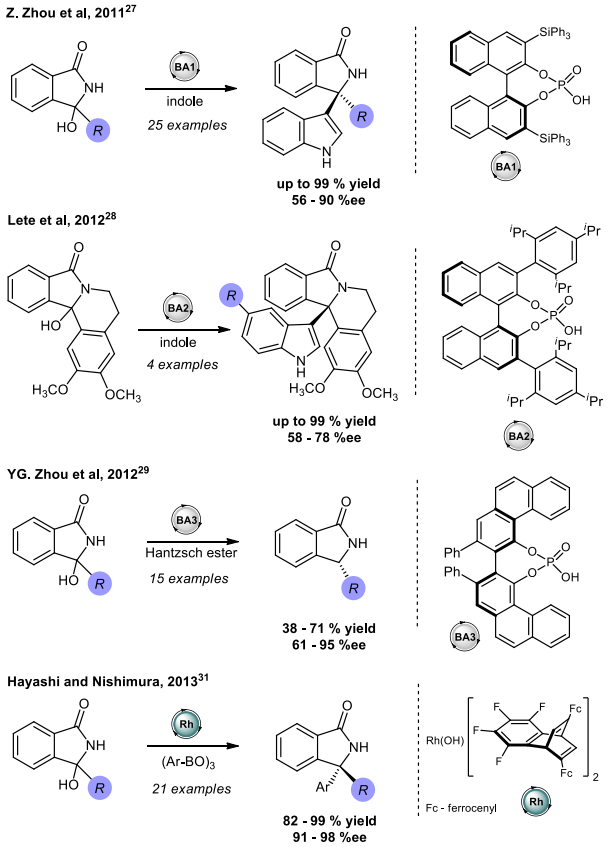
Unsubstituted nitrogen in the final 3-substituted 3-hydroxyisoindolinones is important for their transformation into chiral isoindolinones under Brønsted acid-catalyzed asymmetric reaction conditions (Scheme 2). 3–hydroxyisoindolinone is protonated, followed by the elimination of water. Reactive ketimine intermediate is formed, that forms an ion pair with the anionic catalyst. The chiral catalyst blocks one face of the cation, the nucleophile approaches from the opposite side, and 3,3-disubstituted isoindolinone with tetrasubstituted stereocentre is generated.



Scheme 2 Brønsted acid-catalyzed asymmetric transformation of 3-hydroxyisoindolinones into chiral 3,3-disubstituted isoindolinones.

In the past several years, only a handful of asymmetric transformations have been reported employing 3-substituted 3-hydroxyisoindolinones as substrates.[26] In 2011, the Z. Zhou group reported seminal work in this area. The authors investigated chiral Brønsted acid-catalyzed Friedel-Crafts reaction between 3-substituted 3-hydroxyisoindolinones and indoles (Scheme 3A).[27] Only moderate enantioselectivities were obtained under optimized reaction conditions, and products with excellent enantiomeric purity could be isolated only after recrystallization. Lete et al performed TRIP catalyzed Friedel-Crafts reaction by reacting indoles with cyclic 3-substituted isoindolinone alcohols (Scheme 3B).[28] As with the previous protocol, only moderate enantioselectivities were obtained, while recrystallization of the products led to excellent enantiomeric ratios.

In 2012, Y.G. Zhou et al reported the asymmetric hydrogenolysis of racemic 3-substituted 3-hydroxyisoindolinones with Hantzsch ester, generating 3-substituted isoindolinones in good yields and excellent enantioselectivities (Scheme 3C).[29] The authors investigated the reaction mechanism and provided some insight into the limitations of the transformation. The reaction did not occur when nitrogen on the starting isoindolinone alcohol was substituted, thus proving the importance of N*H* for the reaction outcome. In cases when 3-alkylated 3-hydroxyisoindolinones are employed, generated acyliminium ions can isomerize to corresponding enamines. Hence, the authors submitted 3-alkylideneisoindolinones to the optimized reaction conditions, and no product was afforded. This indicates that the reaction probably occurs directly through the acyliminium intermediate, and that the tautomerization between the imine and the enamine might be irreversible, which would also explain moderate isolated yields of the products. Jia et al performed the same reaction with benzothiazoline as the hydride source. Though high isolated yields of the products were afforded, observed enantioselectivies were moderate, and highly dependant on the structure of the substrates.[30]



Scheme 3 Asymmetric transformations of 3-substituted 3-hydroxyisoindolinones.

Apart from organocatalytic asymmetric transformations, metal-catalyzed protocols are also reported. In 2013, the Hayashi and Nishimura group described a hydroxorhodium/chiral diene complexes as effective catalysts for the asymmetric arylation of 3-aryl 3-hydroxyisoindolinones (Scheme 3D).[31] Arylboroxines, dehydrated derivatives of arylboronic acids, served as dehydrating reagents for the generation of ketimine, as well as arylating reagents for a subsequent arylation by a rhodium catalyst. The Nishimura group built on this principle, and have recently reported the asymmetric [3+2] annulation of 3-hydroxyisoindolinones with internal alkynes by employing a cationic iridium/binap catalyst. The spiroaminoindene products were obtained in a wide range of yields and enantioselectivities, highly dependant on the substituents on the starting materials and reaction conditions. However, the stereochemical outcome of the reaction can be switched by the addition of Brønsted acids.[32]

2 Synthesis of isoindolinone alcohols comprising functional groups

In our group, we are interested in developing asymmetric organocatalytic transformations generating cores of natural compounds. 3-hydroxyisoindolinones have big potential as starting materials for the construction of chiral isoindolinone skeletons, and we believe they have so far been underexploited. As mentioned in the Introduction section, unsubstituted nitrogen in 3-hydroxyisoindolinones is vital for the successful interaction with the chiral catalyst. On the other hand, synthetic protocols that offer a wide range of isoindolinone alcohols comprising various functional groups are limited to *N*-substituted products. The most convenient method for the synthesis of 3-substituted 3-hydroxyisoindolinones possessing unsubstituted nitrogen remains the organometallic addition to phthalimides. However, these protocols are tolerant only for the introduction of alkyl and electron-rich aryl substituents, which substantially limits the substrate scope for further transformations. Hence, before investigating asymmetric transformations that utilize isoindolinone alcohols as starting materials, we were interested in preparing 3-substituted 3-hydroxyisoindolinones with a wide range of functional groups.

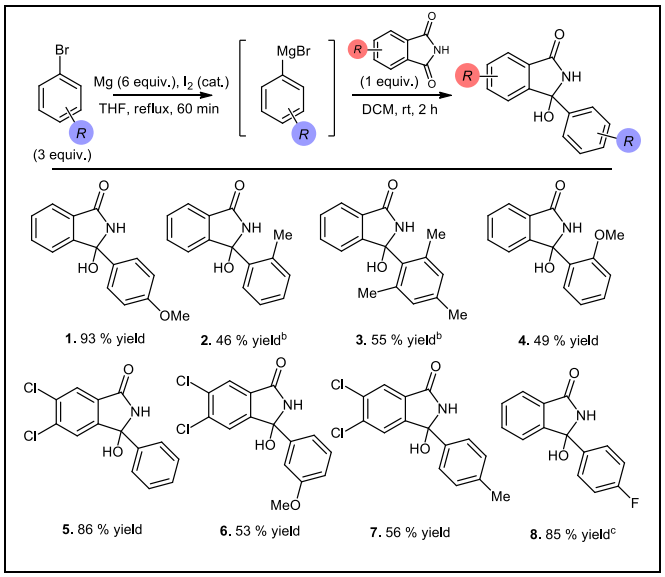
We conducted a synoptic study of the conditions for the preparation of a wide range of isoindolinone alcohols comprising unsubstituted nitrogen in the cyclic amide. Alkyl organometallic reagents are commercially available, and react readily with phthalimides in high yields. Since syntheses of 3–alkyl 3–hydroxyisoindolinones are well described, their preparation was not a part of our study. We identified possible issues for the synthesis of isoindolinone alcohols with electron-poor aryl substituents, as well as with substituents comprising reactive functional groups. In respect to the addition of organometallic reagents to phthalimide, the problem could also be their generation from electron–poor haloarenes. Therefore, we monitored the formation of organometallic reagents by HPLC, as well as their addition to phthalimide. In that way we were not only able to determine when the haloarene was completely activated, but could also detect the progress of its addition to phthalimide.

We started our investigations by employing the Grignard reaction. Representative examples are given in Table 1. After validating the protocol by preparing known 3-substituted 3-hydroxyisoindolinones with electron-rich aryl bromides in high yields (**1**), we turned our attention to more demanding reactants. First, we investigated sterically hindered Grignard reagents. *Ortho* methyl substituted Grignard reagents were generated within an hour, however, isolated yields of their corresponding alcohols were moderate (**2** 46 %, and **3** 55 %). Monitoring these additions to phthalimide by HPLC showed that most of the product was formed after two hours. In the following hours, the reaction substantially slowed down, until it completely stopped after six hours. Yields of the respective products did not improve even when reactions were performed at elevated temperatures, or when the Grignard reagent was added dropwise. In both examples unreacted starting phthalimide was retrieved, which indicates decomposition and/or quenching of the nucleophile.

In order to test whether electron conjugating effect of the *ortho* positioned methoxy group can overcome steric hindrance, we prepared isoindolinone alcohol **4**. Unfortunately, the addition reaction took place in the same fashion as with previous two compounds, affording isoindolinone alcohol **4** in 49 % yield.

Phthalimides bearing a substitution on the aromatic ring are not common reagents in these type of additions, and their 3–hydroxy derivatives were obtained exclusively by cyclization protocols.[36] When 4,5–dichlorophthalimide was employed, 3–hydroxyisoindolinones were readily obtained in good to excellent yields (**5–7**). As in the case with *ortho* methyl substituents, the reaction rapidly slowed down after the initial two hours, before stopping completely after six hours. These results suggest that chlorine substituents lower the reactivity of phthalimide, though possible steric effects cannot be excluded.

Table 1 Addition of Grignard reagents to phthalimides.[a]



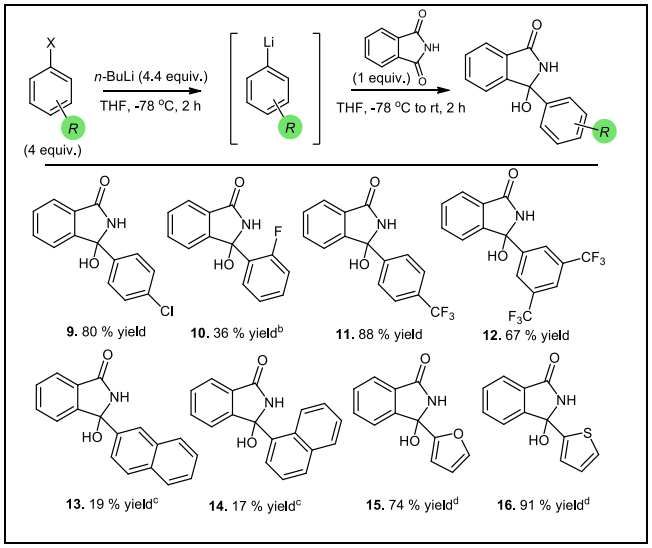
[a] Isolated yields. Conversion of aryl bromide to Grignard reagent monitored by HPLC. [b] Addition of Grignard reagent to phthalimide: 6 hours. [c] Generation of the Grignard reagent: 16 hours.

Next, halogen substituents were tested as the most common functional groups. Unfortunately, only 3–(*p*–fluorophenyl) isoindolinone alcohol **8** could be prepared with this method (85 % yield). When *p*–chlorobromobenzene was used, conversion to its organometallic reagents was only 30 % after 24 hours. Although the conversion of bromochlorobenzenes into chlorophenyl Grignard reagents is reported,[33] the procedure requires use of freshly prepared lithium chloride, and is difficult to handle. On the other hand, the conversion of *o*–fluorobromobenzene was observed only in traces after the same period of time. Therefore, different approach was required for the synthesis of these compounds, so we switched to an organolithium strategy. Table 2 comprises representative examples.

By employing halogen-lithium exchange, haloarenes were successfully converted to their corresponding organolithium reagents, generating 3-substituted 3-hydroxyisoindolinones in good to excellent yields (**9**, **10**). Though it is worth noting that the activation of fluoro-substituted aryl bromides required six hours, while *ortho* substituted organolithiums afforded isoindolinone alcohols in low yields. Trifluoromethylphenyl Grignard reagents are known to be highly reactive and potentially explosive.[34] Hence, trifluoromethylbenzenes were submitted to halogen–lithium exchange. All investigated trifluoromethyl bromides were converted to organolithium reagents within two hours, and afforded corresponding 3–substituted 3–hydroxyisoindolinones in very good yields (**11**, **12**).

Introduction of polycyclic aromatic hydrocarbons was performed using both Grignard and organolithium methods, and in both cases the results were virtually the same. In order to achieve complete conversion, the activation of naphtyl bromides required five hours at room temperature. However, the addition to phthalimide resulted in low yields of the final products (**13**, **14**) regardless of the protocol employed, likely due to steric effects.

Table 2 Addition of organolithium reagents to phthalimide.[a]



[a] X = Br. Isolated yields. Conversion of aryl bromide to organolithium compound monitored by HPLC. [b] Bromine–lithium exchange: 6 hours. Addition to phthalimide: 6 hours. [c] Bromine–lithium exchange: diethyl ether, 5 hours, room temperature. [d] X = H, TMEDA (4.8 equiv.). Hydrogen–lithium exchange: 4 hours.

The halogen–lithium exchange strategy was successfully expanded to direct lithiation protocols, though the activation lasted four hours and required the addition of TMEDA. This methodology offers a significant improvement in yields of furan– (**15**) and thiophene–derived isoindolinone alcohols (**16**) in respect to previously reported procedures.[31]

3 Asymmetric organocatalytic transformations of isoindolinone alcohols

Having obtained a wide range of isoindolinone alcohols, we utilized them in asymmetric transformations as starting materials in the synthesis of *N*(acyl),*S*–acetals. Chiral *N*(acyl),*S*–acetals are an important functional group present in many pharmacologically active and natural compounds (Figure 2). For example, this motif is found in within β–lactam antibiotics,[35] such as penicilin and cephalosporin families, as well as in biologically active[36] and natural compounds.[37] HIV–reverse transcriptase inhibitor **V**[38] especially caught our attention, since its structure is basically 3,3-disubstituted isoindolinone. We reasoned that this inhibitor can be made by an asymmetric addition of thiol to 3–substituted 3–hydroxyisoindolinone, followed by an intramolecular cyclization.

1,2-addition of thiols to imines is the most common method for the synthesis of *N,S*-acetals. Although a widely used protocol, only a handful of its asymmetric variants are reported in literature. These reports include enantioselective addition of thiols to (i) trifluoromethylated aldimines catalyzed by cinchona-derived squaramides,[39] (ii) aldehyde-derived imines under phase-transfer conditions utilizing thiourea-quatenary ammonium salts,[40] and (iii) isatin-derived ketimines were utilizing chiral phosphoric acids[41] and cinchona alkaloids.[42] Antilla et al reported chiral phosphoric acid-catalyzed asymmetric addition of thiols to *N*-acyl imines, and that was the only reported protocol for the direct synthesis of *N*(acyl),*S*-acetals. However, the method had some drawbacks; the substrate scope included only *N*-aldimines that had to be prepared immediately before the reaction, while afforded acyclic *N*(acyl),*S*-acetals were limited to products with tertiary stereocentres. By introducing 3-substituted 3-hydroxyisoindolinones as masked ketimines, we envisaged that the transformation could be expanded to the synthesis of ring-embedded *N*(acyl),*S*-acetals with quaternary carbon stereocentres.

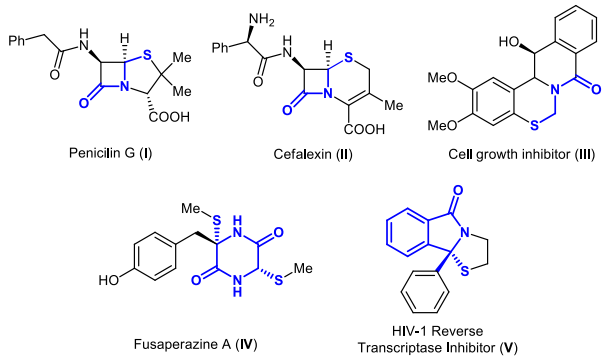


Figure 2 Examples of *N*(acyl),*S*-acetals with biological activity.

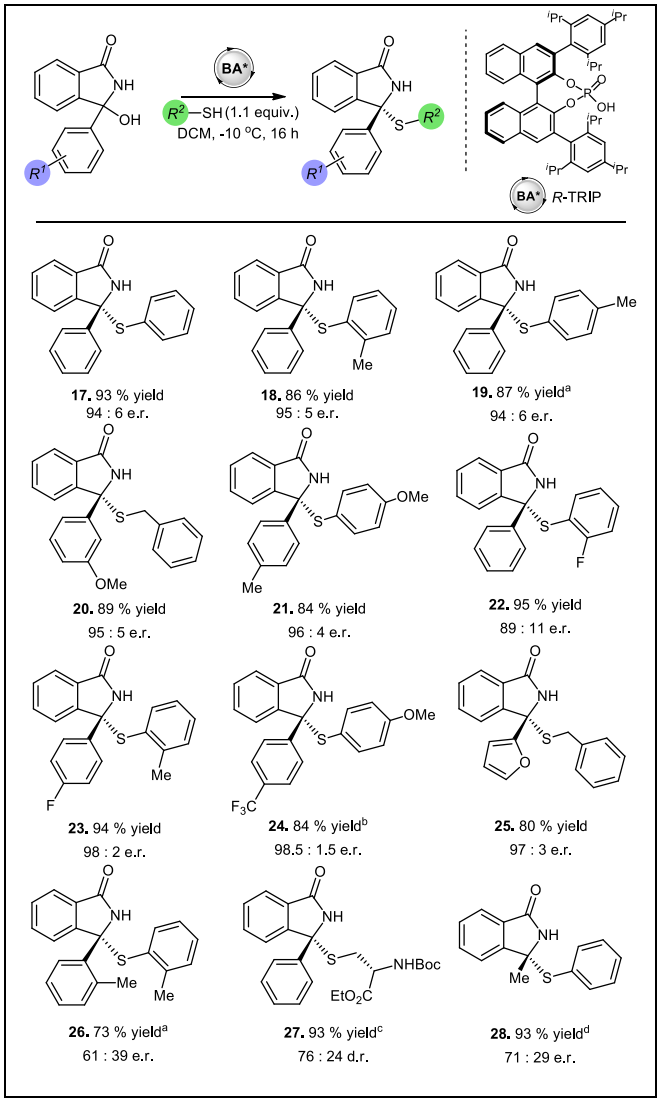
We developed an asymmetric chiral Brønsted acid catalyzed synthesis of chiral *N*(acyl),*S*-acetals.[43] The reaction proceeds via a *N*-acyl ketimine generated *in situ* from 3-substituted 3-hydroxyisoindolinones. Reaction conditions were optimized on a model reaction between 3-phenyl 3-hydroxyisoindolinone and thiophenol. The best yields and enantioselectivities were obtained with *R*-TRIP catalyst in dichloromethane at –10 °C after 16 hours (**17**). Once the optimized reaction conditions were determined, we conducted substrate scope investigation. Selected examples are presented in Table 3.

Various 3-hydroxyisoindolinones reacted successfully with different thiols providing high yields and enantioselectivities. When *ortho*- and *para*-methyl substituted thiophenols, along with aliphatic mercaptanes were used, the high efficiency of the reaction was preserved (**18**–**21**). We observed a slight decrease in enantioselectivities when halogen substituents were place on thiophenol (**22**). On the other hand, the employment of 3–fluorophenyl 3–hydroxyisoindolinones resulted in excellent yields and enantioselectivities, regardless of the nature of the nucleophile (**23**). Introduction of trifluoromethyl substituents required that the reaction had to be performed at room temperature, however, high yields and enantioselectivities were maintained (**24**). The reaction also well tolerated 3–heteroaryl substituents, providing *N*(acyl),*S*-acetals in high yields and enantioselectivities (**25**).

However, the reaction has some limitations. For example, when a significant steric hindrance was created around the reactive centre by employing *ortho*–methyl substituted thiophenol and 3–(*o*–methylphenyl) 3–hydroxyisoindolinone, the reaction time was prolonged to 48 h and gave moderate moderate yield and enantioselectivity (**26**). This result indicates that the steric influence of the chiral Brønsted acid is overridden by the increased steric hindrance around the reactive carbon. In a similar fashion, the reaction did not occur under optimized conditions when the fully protected l–serine was used. The reaction had to be heated to reflux in order to obtain *N*(acyl),*S*–acetal **27**, although in moderate diastereoselectivity.

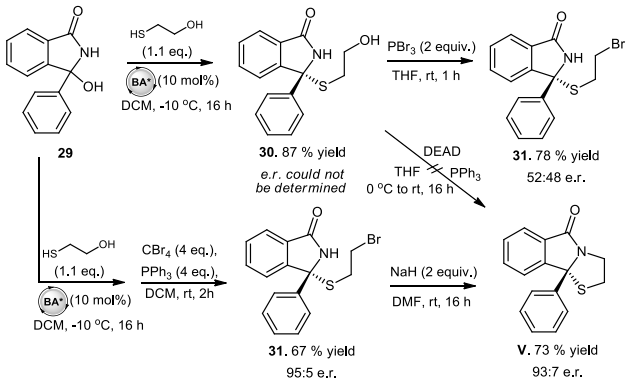
Employing 3–alkylated 3-hydroxy isoindolinones provided *N*(acyl),*S*-acetals in high yields, however, the products were obtained as racemates under optimized reaction conditions. Only when the reaction mixture was cooled to –40 °C were some levels of enantioselectivities observed (**28**). The reason for this result most likely lies in the size of the substituent on position 3 of the 3–hydroxyisoindolinone; small alkyl groups are probably not large enough to create a successful discrimination between *re* and *si* faces of the ketimine intermediate when binding to the catalyst.

Table 3 Chiral phosphoric acid-catalyzed addition of thiols to 3-substituted 3-hydroxyisoindolinones.



[a] 48 hours. [b] Room temperature. [c] 40 °C. [d] –40 °C, 48 hours.

To demonstrate the usefulness of the developed methodology, we decided to utilize it in the preparation of a known HIV-1 Reverse Transcriptase Inhibitor **V** (Scheme 4). We were fortunate that the afforded *N*(acyl),*S*–acetals were (*R*) configuration, the same configuration as the active enantiomer of inhibitor **V**. Employing 2-mercaptoethanol as a nucleophile under optimized reaction conditions yielded 3–substituted 3–mercaptoisoindolinone **30** in very good yield, however, we could not determine the enantiomeric ratio due to high hydrophilicity of the product. We performed an intramolecular Mitsunobu reaction in order to obtain target molecule, however, only starting material was isolated. Different strategy was required, hence, the alcohol **30** was converted to its bromide derivative by employing phosphorus tribromide. Unfortunately, isolated product **31** was afforded as a racemic mixture. Therefore, we switched to the Appel reaction for the substitution of the hydroxy group, and without isolating the alcohol beforehand. Product **31** was obtained in moderate yield after two steps, but with high enantioselectivity. Subsequent 5-exo tet cyclization under basic conditions yielded targeted HIV-1 Inhibitor **V** in good yield, and with the insignificant loss in the enantioselectivity in the final product.



Scheme 4 Synthesis of the HIV-1 Reverse Transcriptase Inhibitor **V**.

During the preparation of this manuscript, Singh et al reported the same asymmetric transformation, however the synthesis of the target inhibitor **V** differs from our approach. The authors used ethyl thioglycolate as a nucleophile, and then reduced the ester, thus affording alcohol **30**. Although unresponsive in our hands, the authors managed to close the ring by employing Mitsunobu reaction, and afford inhibitor **V** in high yield and enantioselectivity.[44]

4 Conclusion

Recently, 3–substituted 3–hydroxyisoindolinones have emerged as convenient substrates for the synthesis of chiral 3–substituted and 3,3–disubstituted isoindolinones, a valuable cores of biologically active molecules and natural compounds. Asymmetric protocols for the generation of these priviledged cores from easy–to–make isoindolinone alcohols could serve as an alternative to widely used cyclization strategies. At the beggining of our research career as an independent group, we chose to work in this field, since the possibility of generating chiral isoindolinone cores from corresponding alcohols offers a big potential and only a handful of asymmetric transformations have been reported in literature. Based on our investigations of asymmetric nucleophilic additions, as well as on results obtained by other groups, we are currently developing more complex principles that have the abbility to generate isoindolinone skeletons comprising two or more chiral centres by employing asymmetric cascade and annulation protocols.

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